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DNA Content and Other Factors Associated With Ten-Year Survival After Resection of Pancreatic Carcinoma

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Background and Objectives: The 5-year survival rates after resection of pancreatic carcinoma have recently increased and are predicted by tumor size, DNA content, and lymph node metastases at the time of resection. However, whether the 10-year survival rates have also increased and are similarly predicted by these factors is not known.

Methods: The influence of preoperative imaging tests, alcohol consumption, cigarette smoking, K-*ras* mutations, anatomic location, details of surgical resection, pathologic findings, and tumor DNA content on survival was tested for 96 patients after a successful resection of a pancreatic carcinoma with 17 patients being followed for more than 5 years.

Results: The 5- and 10-year patient survival rates were 18% and 3%, respectively. Univariate and multivariable analyses showed that tumor DNA content, pathologic tumor size, and lymph node metastases were the strongest prognostic indicators for long-term patient survival, although the importance of tumor size may diminish 2 or more years after resection. Surprisingly, the 11 patients with diploid carcinomas $\geqslant$4 cm had an estimated 10-year survival rate of 36%.

Conclusion: These results show that the 10-year survival rate for pancreatic carcinoma remains very low, although the subset of patients with biologically favorable tumors has a prolonged survival and possible cure after resection. *J. Surg. Oncol. 1998;67:151–159.*

KEY WORDS: **pancreatic cancer; DNA; long-term survival**

INTRODUCTION

The 5-year survival rates reported after surgical resection of pancreatic carcinomas prior to 1983 ranged between 0% and 7% [1–12]. More recently, 5-year survivals have ranged between 7% and 24% for many series [12–25]. This improvement could be due to better surgical technique, selection of healthier patients, earlier stage pancreatic carcinomas for resection, and/or attenuation of the aggressiveness of pancreatic carcinoma [16,26,27]. As to the last possibility, the incidence of pancreatic carcinoma has increased significantly [3,28,29]. This increased incidence has presumably been caused by environmental carcinogens [30–36], leading to the possibility that the predominantly carcinogen-induced pancreatic carcinomas currently treated behave in a more indolent fashion than did pancreatic carcinomas of earlier years. Furthermore, the 5-year patient survival after resection of pancreatic carcinoma is largely predicted by the size and the DNA content of the primary tumor and the presence, or absence, of lymph node metastases at initial resection

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[19,24,37,38]. However, whether these characteristics of the primary carcinomas continue to predict patient survival after 5 years and whether the 10-year survival rates have also improved in the modern era are not known.

To address these issues, we have tested for associations between long-term survival and the details of surgical resection, environmental factors including alcohol consumption, smoking, and putatively carcinogen-induced K-*ras* mutations, as well as pathologic findings and tumor DNA content, in a series of 96 patients with pancreatic carcinoma. The rationale for this study was as follows: tobacco smoke is a known pancreatic carcinogen [29,36], and alcohol may be involved in pancreatic carcinogenesis, but this factor is controversial [31]. Tobacco smoke and other pancreatic carcinogens have been shown to produce K-*ras* mutations in animal models of pancreatic carcinoma [33]; and similarly, carcinogens may play a role in the development of K-*ras* mutations in human pancreatic carcinomas [31,34,36]. If we found that patients who smoked tobacco, drank alcohol, or had carcinomas that harbored K-*ras* mutations had relatively longer survival times than did patients without these factors, support would be provided for carcinogen-induced changes attenuating the aggressiveness of pancreatic carcinoma. Similarly, a finding that the details of operative resection correlated with patient survival would suggest improved surgical techniques are playing a role in the recently reported survival increases.

MATERIALS AND METHODS

Consecutive patients who underwent potentially curative resections for adenocarcinoma of the pancreas at the Johns Hopkins Hospital between 1975 and 1992 were evaluated for inclusion in this study. The short-term results for these patients have been reported previously [19,24]. The histologic criteria for diagnosis of pancreatic carcinoma have been given in detail [19], but can be summarized briefly as follows: 1) there had to be evidence of origin in the pancreas; 2) the neoplasm had to be malignant histologically; and 3) the neoplasm had to demonstrate both epithelial and glandular differentiation. Tumor size was measured in three perpendicular dimensions by the pathologist who dissected the resected specimens, and the middle value of these three dimensions proved to provide the most prognostic information in multivariable analysis (data not shown) and was used to estimate tumor size.

Follow-up was complete for all patients, and the median follow-up time for the nine surviving patients was 81 months (range, 61–208 months). The average age of the patients at the time of resection was 63 years (range, 32–80 years), and 17 patients were followed for 5 or more years after resection. Fifty-two percent (50/96) of the patients were male and 48% (46/96) were female; 83% (60/72) were white and 17% (12/72) were black. Surgical resections included pancreaticoduodenectomies for the 90% (86/96) of the cancers having their origin solely in the head of the pancreas, distal pancreatectomies for the 7% (7/96) of tumors involving the body and tail of the gland, and total pancreatectomies for the 3% (3/96) of cancers involving the entire gland. Adjuvant therapy was not routinely given. A portion of the superior mesenteric or portal vein was resected to provide a potentially curative resection in 14% (13/95) of the cases. Histories of preoperative smoking and alcohol use were evaluated for 83 and 80 patients, respectively, and the preoperative arteriographic findings and computerized axial tomography (CT) scans were evaluated for 40 and 53 patients, respectively. Operative transfusion records were analyzed for 88 patients.

For DNA measurements, pancreatic cancer cells were disaggregated from formalin-fixed, paraffin-embedded tissue blocks, and the Feulgen stain content of at least 300 nuclei per tumor was measured by ''flying spot'' absorption cytometry on coded slides, providing an estimate of the cellular DNA content [19,39,40]. Diploid cells (2C) were assigned a DNA index of 1.0, and the DNA index of aneuploid tumors was calculated as the ratio of the DNA content of the G0/G1 tumor cells to that of the diploid peak. Tumor cell cycle distributions were calculated from rectangular DNA distributions [41]. K-*ras* mutations were determined for 86 cancers by a combination of mutant-enriched PCR analysis and allele-specific oligonucleotide hybridization [34].

The major statistical endpoint of this study was the duration of survival after surgery. Nonparametric estimates of survival probability were made by the product-limit method [42]. Differences between survival distributions were assessed for statistical significance by means of the log-rank statistic [43]. The prognostic effect of dichotomous variables, such as whether a given tumor had a diploid or aneuploid DNA content, was expressed as a hazard ratio, or the risk of death for patients with the variable divided by the risk of death for those without. For continuously distributed prognostic variables, the hazard ratio was expressed per unit change. Hazard ratios were estimated by use of the proportional-hazards regression model [44]. Multivariable proportional-hazards regression models were used for estimation of hazard ratios with simultaneous control for other prognostic factors. Multivariable models were constructed in two stages. First, predictor variables were assessed one at a time in proportional hazards regressions. Variables found to be significant, or nearly so ($P < 0.15$) were entered into multivariable models with backward elimination and re-estimation of hazard ratios, confidence intervals, and *P* values after each step. This process yielded a final ''best'' model. However, we also report some models that retain statistically non-significant effects to illustrate important effects. All *P* values reported are two-sided.

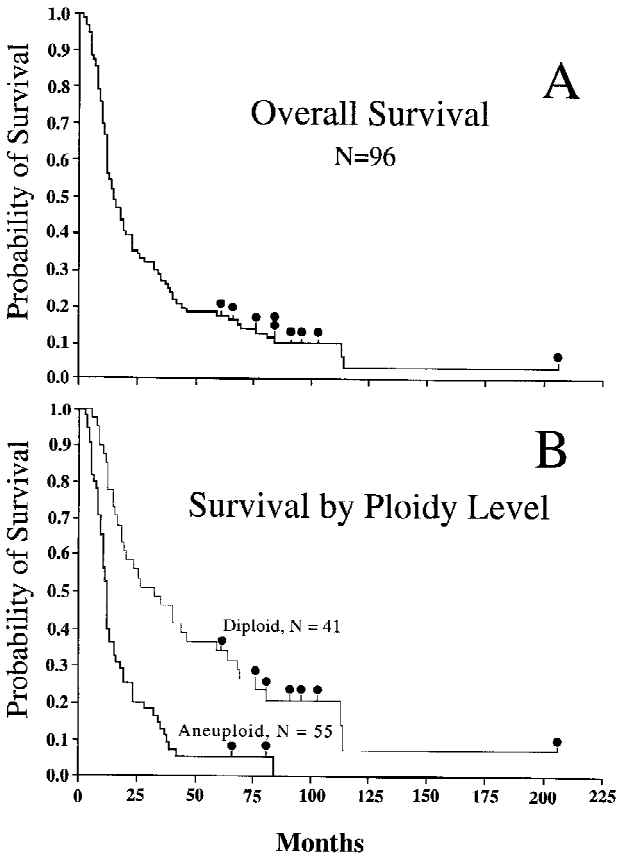

Fig. 1. Kaplan-Meier survival curves for 96 patients after potentially curative resection for pancreatic carcinoma **(A)** and for patient survival stratified by diploid or aneuploid tumor DNA content **(B).** Forty-one patients had diploid pancreatic carcinomas, and 55 patients had aneuploid pancreatic carcinomas. ●, time of last follow-up of surviving patients.

RESULTS

The overall survival for the entire series is shown in Figure 1A and Table I. The median survival for all patients in the series was 10 months. The 5-year overall survival rate was 18%, and the 10-year overall survival rate was estimated at 3%. The exact cause of death was available for 82 of the 87 patients who died: all but one of the 75 deaths in the first 5 years after resection, and all seven deaths between 5 and 10 years after resection, were due to recurrent cancer. The death rates between 0 and 5 years and those between 5 and 10 years were essentially the same (~82%, Fig. 1A), showing that surviving 5 years after resection for pancreatic carcinoma means little for predicting cure of this disease.

The tumor ploidy level was a strong predictor of long-term patient survival. Forty-three percent (41/96) of the carcinomas were diploid, and 57% (55/96) were aneuploid. The survival rates of the patients with diploid and aneuploid carcinomas are shown in Figure 1B and Table I. At 5 years, 34% of the patients with diploid cancers were alive, compared to 5% of the patients with aneuploid cancers. At 10 years, only 7% of the patients with diploid cancers were alive, whereas none of the patients with aneuploid carcinomas had survived (Fig. 1B, Table I). The median percentage of S-phase cells for all 96 patients was 8%, and 14 of the 17 patients who survived beyond 5 years had percentages of S-phase cells below this value.

TABLE I. Five- and Ten-Year Survivals of 96 Patients With Pancreatic Carcinoma After Potentially Curvative Resection

Group	No. of patients	5-year survival (95% CI[a])	10-year survival (95% CI)
All patients	96	18% (10–25)	3% (0–9)
Aneuploid cancers	55	5% (0–11)	0%
Diploid cancers	41	34% (20–49)	7% (0–19)
Node-positive	62	10% (2–17)	0%
Node-negative	34	32% (17–48)	9% (0–24)
⩾4 cm, aneuploid	16	0%	0%
⩾4 cm, diploid	11	36% (8–65)	36% (8–65)
<4 cm, aneuploid	39	8% (0–16)	0%
<4 cm, diploid	30	33% (16–50)	0%

[a]CI, confidence interval.

Lymph node metastases were a grave prognostic sign (Fig. 2A, Table I). The percentage of lymph nodes with metastases was a stronger prognostic variable than either the number of cancer-positive lymph nodes or when the presence, or absence, of lymph node metastases was treated as a dichotomous variable (Table II). The 35% (34/96) of the patients who did not have lymph node metastases had estimated 5- and 10-year survival rates of 32% and 9%, respectively (Fig. 2A, Table I), whereas the 65% (62/96) of the patients who had lymph node metastases had estimated 5- and 10-year survivals of 10% and 0%, respectively. All of the six node-positive patients who survived for 5 years or more had three or fewer lymph node metastases; three of these patients succumbed to recurrent tumor at 69, 84, and 113 months, respectively, and three were still alive at 66, 91, and 103 months after resection.

The association of tumor size with patient survival showed a curious result (Fig. 2B). At 5 years, the 47% (45/96) of the patients with tumors ⩽2.5 cm had an estimated survival rate of 27%, compared to 10% for the 53% (51/96) of the patients with cancers >2.5 cm. At 10 years, however, none of the patients with the smaller tumors were estimated to have survived, whereas 5% of the patients with the larger tumors were estimated to be alive. When looked at in more detail, 44% (20/45) of the patients with tumors ⩽2.5 cm had succumbed within 2 years of resection, compared to 82% (42/51) of the patients with carcinomas >2.5 cm. After 2 years, however, 80% (20/25) of the patients with carcinomas ⩽2.5 cm had died, compared to 56% (5/9) of the patients with carcinomas >2.5 cm. Figure 3 shows a Kaplan-Meier survival plot for patients with large (⩾4 cm) and small

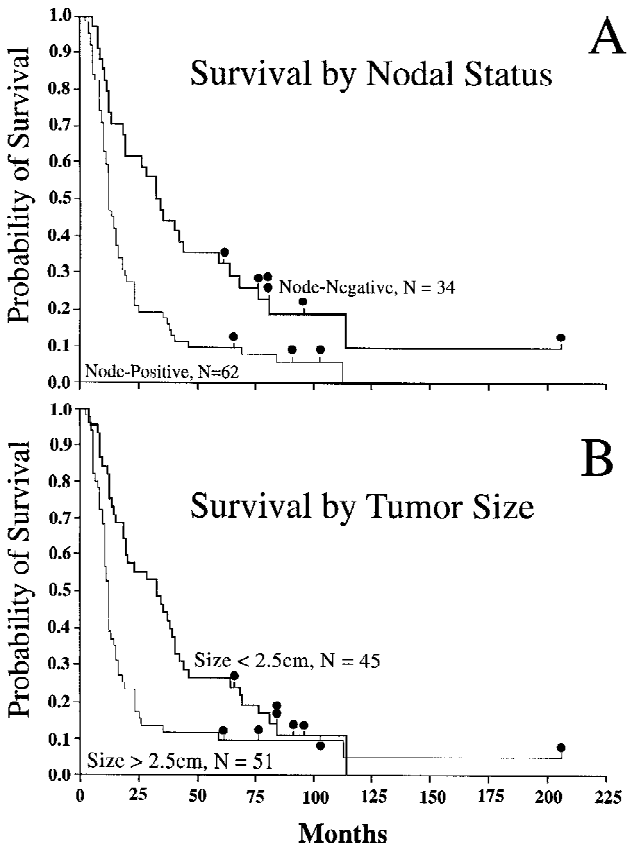

Fig. 2. Kaplan-Meier survival curves for 96 patients after potentially curative resection for pancreatic carcinoma, with patient survival stratified by lymph-node-positive and -negative carcinomas (A) and by tumor size (B). **A:** Thirty-four patients did not have any lymph node metastases, and 62 patients had at least one tumor-positive lymph node. **B:** Forty-five patients had small (≤2.5 cm) carcinomas, and 51 patients had large (>2.5 cm) carcinomas. ●, time of last follow-up of surviving patients.

(<4 cm) pancreatic carcinomas also stratified by tumor ploidy level. The 16 patients with aneuploid carcinomas ≥4 cm had a median survival of only 8 months, and all of these patients died from cancer within 23 months of resection. Surprisingly, the 11 patients with diploid cancers ≥4.0 cm had a median survival of 27 months and an estimated 5- and 10-year survival of 36%, with four patients being tumor-free at 61, 76, 103, and 208 months after resection (Fig. 3, Table I). Nine of 11 of these large diploid cancers had percentages of S-phase cells below the median value of 8%, and the four patients surviving for 5 or more years had S-phase percentages of 6% or less. The 39 patients with aneuploid cancers <4 cm had a 5-year survival of 8% and an estimated 10-year survival of 0% (Table I), although two patients in this group remain tumor-free at 66 and 81 months. The 30 patients with diploid cancers <4 cm had a 33% 5-year survival, but an estimated 10-year survival of 0%, although three patients were tumor-free at 81, 91, and 96 months after resection (Fig. 3).

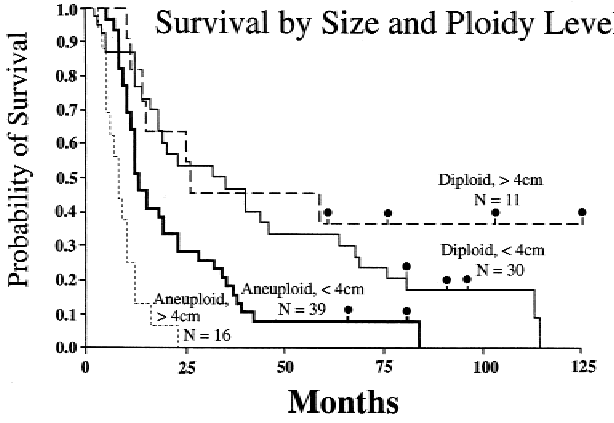

Fig. 3. Kaplan-Meier survival curves for 11 patients with large (≥4 cm) diploid pancreatic carcinomas; 30 patients with small (<4.0 cm) diploid pancreatic carcinomas; 39 patients with small (<4 cm) aneuploid carcinomas; and 16 patients with large aneuploid cancers. ●, time of last follow-up of surviving patients.

We performed both univariate and multivariable analyses for the prognostic value of the different factors over the entire duration of the study; during this time period, a sufficient number of patient deaths occurred to allow valid statistical conclusions to be drawn. Tumor ploidy levels, pathologic tumor size, the presence of lymph node metastases, the percentages of tumor cells in the different phases of the cell cycle (% of G0/G1-, S-, and >G2/M-phase cells), and soft-tissue invasion were significant prognostic factors when evaluated by univariate analysis (Table II). The following factors did not show statistical significance as prognostic indicators for patient survival in univariate analysis (Table III): smoking history, history of alcohol use, K-*ras* mutations, the number of transfusions given during operation, the anatomic location of the carcinoma (head, body, tail, or the entire gland), having to resect a portion of the superior mesenteric or portal vein, the presence of positive surgical margins, the three perpendicular tumor diameters measured by CT scan, and abnormal preoperative arteriograms. There was no significant heterogeneity of patient survival when the results of all of the surgeons were analyzed as a group by univariate analysis (data not shown). Forty-seven of the resections were done by the senior surgeon, and the remaining resections by 16 different surgeons. There were significantly higher proportions of smaller carcinomas and Caucasians among the patients resected by the senior surgeon. The patients resected by the senior surgeon had a slightly improved survival compared to all other patients ($P = 0.1$, Table III).

Table IV shows some of the multivariable models used for ranking the relative importance of the factors found to be significant prognostic indicators in univariate analysis. The first panel shows that ploidy level, tumor size, percentage of positive lymph nodes, and percentage of

TABLE II. Pancreatic Cancer: Estimated Hazard Ratios for Death, With Significance Levels, for the Possible Prognostic Variables Showing Significance ($P < 0.05$) in Univariate Analysis

Variable	% (N)[a] Positive	Hazard ratio	95% CI[b]	*P* value[c]
Aneuploid vs. diploid	57 (55/96)	2.65	1.67–4.18	0.0001
Tumor size[d]	—	1.14	1.01–1.29	0.04
Nodes positive vs. negative	65 (62/96)	2.11	1.33–3.36	0.002
N of positive nodes	—	1.17	1.08–1.26	0.0001
% of positive nodes[e]	—	4.62	2.11–10.13	0.0001
% G0/G1 cells[f]	—	0.97	0.96–0.99	0.004
% S-phase cells	—	1.05	1.02–1.07	0.0002
% >G2/M cells	—	1.14	1.00–1.29	0.05
P1 (S + G2/M + >G2/M)[g]	—	1.03	1.01–1.04	0.005
Soft-tissue invasion	59 (56/95)	1.78	1.14–2.79	0.01

[a]% and frequency for dichotomous variables.
[b]CI, confidence interval.
[c]*P* value for the hypothesis that the hazard ratio equals 1.
[d]Hazard ratio for each centimeter of the middle pathologic tumor diameter.
[e]Hazard ratio for % of cancer-positive lymph nodes. For % positive nodes, 1 unit change represents the difference between no positive nodes and all positive nodes.
[f]Hazard ratio for each % of G1, S, G2/M, or >G2/M cells.
[g]PI, proliferative index or $\sum$ (S + G2/M + >G2/M).

S-phase cells all provide independent and significant prognostic information, whereas the presence of soft tissue invasion and the percentages of >G2/M and G0/G1 tumor cells do not, as can be seen in the multivariable models shown in the second and third sections of Table IV. The fourth section of Table IV shows that ploidy level, tumor size, percentage of positive nodes, and the percentage of S-phase cells are the strongest prognostic factors in this series. Table V shows the best multivariable model for long-term, overall survival after resection of carcinoma of the pancreas. Ploidy level, the percentage of S-phase tumor cells, the percentage of tumor-positive lymph nodes, and tumor size are all independent and significant prognostic factors. Thus, the longer follow-up in this study confirms the importance of these factors that was found previously when these patients were followed for shorter time periods [19,24].

DISCUSSION

This series of 96 pancreatic carcinoma patients, in which the survivors were followed for a median of 81 months after resection, confirms that DNA content, pathologic tumor size, and lymph node metastases are the most important prognostic determinants of patient survival after resection of pancreatic carcinoma (Table V)[19,24,43,44]. Although tumor size remains a statistically important and independent prognostic determinant in the present study (Tables IV, V), the longer follow-up data suggest that tumor size may not be important as a prognostic variable for those patients who have survived 2 or more years after resection. Most importantly, four of our patients with large cancers ($\geqslant$4 cm) that had diploid tumor DNA content are currently tumor-free at 61, 76, 103, and 208 months after resection (Fig. 3). Furthermore, each of these large, diploid tumors in these long-term survivors had a low percentage of S-phase cells (<6%), a cell-cycle parameter that is associated with a low tumor growth rate. These findings suggest the existence of a class of large, slowly growing pancreatic carcinomas with a genetically stable DNA content that have a relatively favorable prognosis.

The prognostic information potentially available from tumor size, DNA measurements, and lymph node status currently has very limited practical application for improving the care of patients with pancreatic carcinoma. First, a suitable technique for accurately measuring the DNA content of pancreatic carcinoma cells must be employed. Image analysis DNA measurements, which involve the measurement of the individual absorbances of Feulgen stained nuclei fixed onto slides, may be superior to flow cytometry in measuring the DNA content of pancreatic carcinomas [45]. Further, among the image analysis techniques available for use, it is possible that DNA measurements made with ''flying spot'' cytometers may be somewhat more precise than those made with ''video microscopy'' systems [19,24,46,47]. The DNA measurements could be used for stratification for adjuvant therapy and there is some preliminary indication that aneuploid pancreatic carcinomas may respond more favorably to adjuvant chemotherapy than diploid cancers (W.C. Dooley, personal communication). DNA measurements of pancreatic carcinoma cells obtained from fine

TABLE III. Pancreatic Cancer: Estimated Hazard Ratios for Death, With Significance Levels, for the Possible Prognostic Variabales Which Did *Not* Show Significance ($P > 0.05$) in Univariate Analysis

Variable	% (N)[a] Positive	Hazard ratio	95% CI[b]	*P* value[c]
Age at diagnosis	—	1.01	0.99–1.03	0.53
White vs. black	83 (60/72)	0.87	0.45–1.68	0.68
Female vs. male	48 (46/96)	1.03	0.68–1.57	0.89
No alcohol vs.				
occasional use	49 (42/86)	0.94	0.55–1.60	0.82
regular use	8 (7/86)	0.91	0.37–2.22	0.83
heavy use	13 (11/96)	1.08	0.53–2.21	0.83
Non-smoker vs.				
previous smoker	43 (36/83)	1.29	0.74–2.24	0.37
current smoker	28 (23/83)	1.19	0.64–2.19	0.59
Wild-type *K-ras* vs.				
mutated *K-ras*	84 (64/76)	0.70	0.35–1.43	0.33
Largest CT dimension				
(53 patients)	—	1.02	0.81–1.24	0.98
Abnormal arteriogram	12 (5/40)	1.15	0.40–3.29	0.79
Pancreatic head vs.				
tail and body	7 (7/96)	0.65	0.30–1.41	0.27
whole gland	3 (3/96)	2.37	0.58–9.68	0.23
Transfusion (per unit)	—	1.06	0.95–1.19	0.31
Portion of SMV[d]				
resected	14 (13/95)	1.49	0.82–2.71	0.19
Surgical margin				
initially negative vs.				
revised negative	12 (11/95)	1.04	0.53–2.02	0.91
margin positive	9 (9/95)	0.97	0.44–2.11	0.93
Surgeon[e]	49 (47/96)	0.70	0.46–1.07	0.10

[a]% and frequency for dichotomous variables.
[b]CI, confidence interval.
[c]*P* value for the hypothesis that the hazard ratio equals 1.
[d]SMV, superior mesenteric or portal vein.
[e]Hazard ratio for the results of the 47 resections done by the senior surgeon compared to the 49 resections done by 16 other surgeons.

TABLE IV. Pancreatic Cancer: Estimated Hazard Ratios for Death, With Significance Levels, for Multivariable Proportional-Hazards Regression Models (Each Panel Represents a Separate Multivariable Model)

Variable	Hazard ratio	95% CI[a]	*P* value[b]
Aneuploid vs. diploid	1.62	0.91–2.90	0.10
Tumor size[c]	1.15	1.01–1.32	0.03
% of positive nodes[d]	3.51	1.42–8.69	0.006
Soft-tissue invasion	1.30	0.81–2.10	0.28
% S-phase cells[e]	1.05	1.00–1.11	0.07
% >G2/M cells	0.94	0.78–1.14	0.54
% G1-phase cells	1.01	0.97–1.04	0.73
Aneuploid vs. diploid	1.62	0.91–2.89	0.10
Tumor size	1.15	1.01–1.31	0.03
% of positive nodes	3.54	1.43–8.77	0.006
Soft-tissue invasion	1.29	0.81–2.08	0.28
% S-phase cells	1.04	1.00–1.08	0.03
% >G2/M cells	0.93	0.78–1.12	0.45
Aneuploid vs. diploid	1.61	0.90–2.87	0.11
Tumor size	1.15	1.01–1.31	0.03
% of positive nodes	3.50	1.42–8.62	0.006
Soft-tissue invasion	1.31	0.82–2.10	0.26
% S-phase cells	1.03	1.00–1.07	0.03
Surgeon[f]	0.67	0.43–1.04	0.08
Aneuploid vs. diploid	1.76	1.00–3.11	0.05
Tumor size	1.20	1.05–1.36	0.0007
% of positive nodes	3.65	1.52–8.80	0.004
% S-phase cells	1.03	1.00–1.06	0.04

[a]CI, confidence interval.
[b]*P* value for the hypothesis that the hazard ratio equals 1.
[c]Hazard ratio for each centimeter of the middle pathologic measurement of tumor size.
[d]Hazard ratio for % of cancer-positive lymph nodes. For % positive nodes, 1 unit change represents the difference between no positive nodes and all positive nodes.
[e]Hazard ratio for each % of G1, S, G2/M, or >G2/M cells.
[f]Hazard ratio for results of the 47 resections done by the senior surgeon compared to the 49 resections done by 16 other surgeons.

needle aspirates [48] could potentially help to identify those patients who are likely to have a poor outcome after resection and thereby allow the selection of appropriate candidates for preoperative neoadjuvant therapies or other palliative measures. For example, the 16 patients with the large (≥4 cm), aneuploid pancreatic carcinomas in this series had dismal outcomes, with the longest survivors dying of recurrent cancer at 12, 16, and 23 months after resection (Table I, Fig. 3). Unfortunately, in our study the preoperative CT-scan estimates of tumor size were not a significant prognostic indicator (Table III), but hopefully this will change with the arrival of improved imaging modalities [49].

The decrease in operative mortality for resection of pancreatic carcinoma in the modern era has led to some improvement in overall patient survival, but cannot completely explain the increased 5-year survivals currently reported [1–25]. Tumor-negative margins, low transfusion requirements, resection of part of the superior mesenteric or portal vein, and the anatomic location of the cancer did not have any significant influence on patient survival by univariate analysis (Table III). These findings argue against the possibility that the recent improvements in the 5-year survival rates of patients with pancreatic carcinoma after resection are primarily due to more complete surgical removal of the cancers. However, relatively subtle differences in outcomes secondary to differences in the surgical technique, especially striving for tumor-free margins, might be detected in larger series addressing these questions (Table III). A recent report has shown that combining pancreatic, bile duct, duodenal, retroperitoneal soft-tissue margins, and the need to resect vascular structures into one variable does provide some prognostic information in univariate analysis, although this variable was not significant in multivariable analysis when other prognostic indicators were evaluated [24]. It was not clear whether the borderline improved survival for the patients resected by the senior

TABLE V. Multivariable Proportional-Hazards Regression Model Showing the Strongest Prognostic Factors for Survival After Resection of Pancreatic Carcinoma, Stratified by Surgeon

Variable	Hazard ratio	95% CI[a]	*P* value[b]
Aneuploid vs. diploid	1.83	0.95–3.54	0.07
Tumor size[c]	1.14	1.00–1.31	0.06
% of positive nodes[d]	3.52	1.28–9.67	0.01
% of S-phase cells	1.04	1.00–1.08	0.05

[a]CI, confidence interval.
[b]*P* value for the hypothesis that the hazard ratio equals 1.
[c]Hazard ratio for each centimeter of the middle pathologic measurement of tumor size.
[d]Hazard ratio for % of cancer-positive lymph nodes. For % positive nodes, 1 unit change represents the difference between no positive nodes and all positive nodes.

surgeon was attributable to surgical technique or selection factors. Several uncontrolled series have also recently suggested that formal lymphadenectomies and/or ''radical pancreatectomies'' may improve the survival of patients with pancreatic carcinoma [50–56]. None of the patients in our series had formal lymphadenectomies, and all of the 62 patients with lymph node metastases were estimated to have succumbed to recurrent cancer within 113 months of resection (Fig. 2A). Taken together, these results suggest that controlled trials are needed for evaluation of the possible benefits of formal lymph node dissections, as well as other aspects of surgical technique, in the treatment of pancreatic carcinoma.

Survival was not influenced by alcohol consumption or cigarette smoking, or by the presence of K-*ras* mutations in the carcinomas (Table III). These findings suggest that the mechanism of transformation does not dictate the long-term survival of pancreatic carcinoma patients, and they argue, albeit indirectly, against the possibility that pancreatic carcinoma is currently being attenuated by environmental factors. Even if attenuation is playing a partial role in the increased 5-year survivals reported for many contemporary series, it does not seem that pancreatic carcinoma is becoming, at least as yet, a more indolent tumor in terms of 10-year survival or possible cure, because the 10-year estimated survival was only 3% in this series (Table I, Fig. 1A). However, this 10-year survival figure may improve with longer follow-up of the more recently resected patients. Although only one of the 38 patients resected between April 1975 and October 1987 still survives in our series, eight of the 58 patients resected between November 1987 and January 1991 are still alive and tumor-free 5 or more years after surgery. We hope that these patients will eventually prove to have a higher 10-year survival rate.

Thus, it is possible that some sort of selection, improved surgical techniques, and/or environmental factors attenuating this disease may all play a role in the improved 5-year survivals reported after resection of pancreatic carcinomas in the modern era [12–25]. There has been no decrease in the stages of pancreatic carcinomas resected at this institution over the last three decades [24], thus arguing against the possibility that the selection of earlier-stage carcinomas is responsible for the increased 5-year survivals in the modern era. However, ''more fit'' patients, as measured by the Karnofsky index, have a lower morbidity and mortality after resection of pancreatic carcinomas [57]. If ''more fit'' patients have a better chance of surviving 5 years than ''less fit'' patients with similarly staged cancers, and if relatively greater numbers of ''fit'' patients were selected for resection in the modern era compared to earlier times, this might partially explain the current 5-year survival increases. If this factor was playing an important role, it would still be expected that the 10-year survival rates would be approximately the same in the modern and earlier eras, as seems to be the case (Fig. 1A), because patient ''fitness'' could not ultimately control cancer recurrence. The observation that 81 of the total of 82 patient deaths for which the exact cause of death was obtainable were due to recurrent cancer and not to other causes suggests that a relatively ''fit'' cohort of elderly patients (median age 63 years) was selected for resection in our series.

Regardless of the mechanism(s) responsible for the relatively high 5-year survivals currently reported in this and other contemporary series [12–25], the finding of a relatively low 10-year survival rate does not diminish the significant improvement that has occurred in recent years in the treatment of pancreatic carcinoma. Resection can now be performed safely and with low morbidity, and it provides excellent palliation for most patients without the need for stent placements, stent changes, and numerous subsequent procedures attendant to nonoperative means of palliation [58]. The 5-year survival results have been improving steadily for the last three decades [24], and parallel increases in the 10-year survival and cure rates may be expected to eventually occur. Also, the patients in this series were resected prior to the widespread application of adjuvant therapy, which improves short-term patient survival and may have beneficial long-term effects [47]. Even today, complete resection of pancreatic carcinomas provides the only realistic chance for cure for a small number of patients. Hopefully, these benefits of resection will soon be combined with new advances in early detection and in other therapies that will further advance the treatment of this deadly disease.

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